Original Research Article

Antiepileptic drug prescribing before, during and after pregnancy: a study in 7 European regions

Running header – Antiepileptic drug prescribing during pregnancy

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Key words
anticonvulsants; pregnancy; drug utilization; electronic health records

Key points

- The prevalence of antiepileptic drug prescribing before, during and after pregnancy varies between different regions of Europe.
- Within Europe, variations exist in the specific antiepileptic drugs most commonly prescribed.
- Evidence that a proportion of AED prescriptions are being stopped during pregnancy rather than before pregnancy, as well as low levels of folic acid co-prescribing, suggests that many pregnancies are either unplanned or that full preconception care is not received by many women.

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Conflict of interest statement

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Prior postings and presentations

The results of this research have been presented as an oral presentation at the 30th International Conference of Pharmacoepidemiology and Drug Safety in Taipei in October 2014 and at the EURODURG conference in The Netherlands in August 2014.

Abstract

Purpose To explore antiepileptic drug (AED) prescribing before, during and after pregnancy as recorded in seven population-based electronic healthcare databases.

Methods Databases in Denmark, Norway, the Netherlands, Italy (Emilia Romagna/Tuscany), Wales, and the Clinical Practice Research Datalink, representing the rest of the UK, were accessed for the study. Women with a pregnancy starting and ending between 2004 and 2010, which ended in a delivery, were identified. AED prescriptions issued (UK) or dispensed (non-UK) at any time during pregnancy and the 6 months before and after pregnancy were identified in each of the databases. AED prescribing patterns were analysed and the choice of AEDs and co-prescribing of folic acid were evaluated.

Results In total, 978,957 women with 1,248,713 deliveries were identified. In all regions, AED prescribing declined during pregnancy and was lowest during the third trimester, before returning to pre-pregnancy levels by 6 months following delivery. For all deliveries, the prevalence of AED prescribing during pregnancy was 51 per 10,000 pregnancies (CI_{95}49-52) and was lowest in the Netherlands (43/10,000 CI_{95}33-54) and highest in Wales (60/10,000 CI_{95}54-66). In Denmark, Norway and the two UK databases lamotrigine was the most commonly prescribed AED, whereas in the Italian and Dutch databases carbamazepine, valproate and phenobarbital were most frequently prescribed. Few women prescribed AEDs in the 3 months before pregnancy were co-prescribed high dose folic acid: ranging from 1.0% (CI_{95}0.3-1.8) in Emilia Romagna to 33.5% (CI_{95}28.7-38.4) in Wales.

Conclusion The country differences in prescribing patterns may suggest different use, knowledge or interpretation of the scientific evidence base. The low co-prescribing of folic acid indicates that more needs to be done to better inform clinicians and women of childbearing age taking AEDs about the need to offer and receive complete preconception care.

Introduction

The older antiepileptic drugs (AEDs), when taken during early pregnancy, are associated with a risk of major congenital anomalies two to three times greater than that of the general population,[1, 2] although this varies with AED.[3, 4] Sodium valproate has also been associated with impaired cognitive function and developmental delay in the offspring.[5] The teratogenic effects outside the epilepsy indication are uncertain, but it is advised to take a precautionary approach. Over the last two decades a number of new AEDs have been introduced and, for some, the safety profiles indicate a lower risk of teratogenicity,[6] whilst for others they are yet to be fully determined.[7, 8]

Three to four pregnancies in every thousand involve women with epilepsy.[9] The risk of seizure recurrence means it is often not appropriate to discontinue treatment, and some women require more than one AED (polytherapy) to obtain optimum seizure control. As some AEDs are more effective than others at controlling particular types of seizures, with risks to both mother and fetus from poor seizure control, it is not always possible to prescribe pregnant women the product with the most favourable safety profile in relation to teratogenicity.[10]

In addition to epilepsy, some AEDs are licensed or prescribed off-label to treat other conditions including trigeminal neuralgia, neuropathic pain and as prophylaxis of bipolar disorder, migraine, depression and generalised anxiety disorders.[11] Women taking AEDs are recommended to take folic acid prior to conception and in the first trimester, as some AEDs may alter folate metabolism or absorption.[12] This study aimed to assess the extent and nature of AED prescribing, regardless of indication, during and around pregnancy in seven population-based electronic healthcare databases in Europe between 2004 and 2010. This study forms part of EUROmediCAT, a Seventh Framework Programme study funded by the European Commission that aims to make more systematic use of electronic healthcare databases in combination with EUROCAT congenital anomaly registry data[13] for reproductive safety evaluation.

Methods

Setting

Seven population-based electronic healthcare databases contributed to the study; two in Italy (Tuscany[14]/Emilia Romagna[15]), two in the United Kingdom (the Secure Anonymised Information Linkage Databank in Wales [16] and the UK-wide Clinical Practice Research Datalink with data from Wales excluded),[17] and one in each of Denmark,[18, 19] Norway[20, 21] and the Netherlands[22] (Table 1). Data sources that involved the linkage of multiple databases will be referred to as a single database for the remainder of this paper; for example, the Norwegian Medical Birth Registry was linked to the Norwegian Prescription Database. A more detailed description of the databases can be found elsewhere.[23] Ethical and data access approvals were obtained for each database from the relevant governance infrastructures.

--------- Insert Table 1 here ---------

Study population

All databases followed a common protocol. Within each database pregnancies which started and ended between 1 January 2004 and 31 December 2010 were identified (except for Denmark and Norway where inclusion dates were 1-Jan-2004 to 31-Dec-2009 and 1-Jul-2004 to 31-Dec-2010 respectively). Pregnancies were excluded if they did not end in a delivery (live/stillbirth) and if the woman was not followed in the database, which captured prescription data, for the six months before pregnancy, throughout pregnancy and for at least six months following delivery. For each pregnancy ending in a delivery, the start date of the pregnancy was identified or estimated based on additional data including gestational age at birth and the date of delivery (Table 1). For each pregnancy, the start and end of each pregnancy trimester was determined; trimester one was from the start of pregnancy through to 90 days gestational age, trimester two was from 91 until 188 days and trimester three was from 189 days gestational age until delivery.

Exposure

All prescriptions for AEDs in the 6 months before pregnancy, during pregnancy and in the 6 months following delivery were identified. In the UK databases this included all AED prescriptions issued whilst in the other databases it was only AED prescriptions actually dispensed. AEDs were defined as those with an Anatomical Therapeutic Classification (ATC) code starting N03A or N05BA09, in addition to N05BA01, N05BA06, N05CD08 and N05CC05 when prescribed as a non-oral preparation. AEDs identified included, but were not limited to, barbexaclone, carbamazepine, clonazepam, diazepam, ethosuxamide, phenobarbital, phenytoin, primadone and valproate, categorised as 'old' AEDs and felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin and zonsamide, categorised as 'newer' AEDs. A full list of AEDs and their availability in each of the regions during the study period can be found in Table S1. Multiple therapy prescribing, reflecting either polytherapy or switching, was defined as a prescription for two or more different AEDs during a 3-month time period. Prescriptions issued for folic acid (ATC B03BB01/B03BB51) were also identified.

Analyses

The prevalence of prescribing was calculated, for each AED and each database, for the 6 months leading up to pregnancy, during pregnancy and the 6 months following delivery. The AED prescribing prevalence was also calculated for each pregnancy trimester and for two 3-month time periods both before and after pregnancy and reported per 10,000 deliveries.

Monotherapy and multiple-therapy prescribing were compared between databases. The percentage of AED exposed deliveries prescribed specific AEDs and changes in prescribing between 2004 and 2009 were evaluated. The percentage of pregnancies where the women received only a single AED prescription during the entire 21-month time period was determined and maternal age at the start of pregnancy was evaluated stratified by AED. The percentage of AED exposed pregnancies where the woman received a co-prescription for folic acid, within the same 3-month period, was calculated.

Results

In total, 978,957 eligible women with 1,248,713 deliveries were identified. The mean maternal age at the start of pregnancy ranged from 27.6 years in Wales to 32.2 years in Emilia Romagna (Table 2). Overall, AED prescribing prevalence during the 6 months before pregnancy was 64/10,000 deliveries (CI_{95}62-65) and was lowest in Denmark and highest in the UK (Table 2). During pregnancy, the AED prescribing prevalence was 51/10,000 deliveries (CI_{95}49-52). In all databases, prescribing declined during the first and second trimesters of pregnancy (Figure 1). By four to six months post-delivery, AED prescribing had returned to pre-pregnancy levels in the Dutch and both UK databases (Figure 1), whilst in the Danish, Italian and Norwegian databases AED prescribing was 10% to 20% lower than during the four to six months before pregnancy. When looking at the entire 21-month time period, the prevalence of prescribing was highest in the Tuscany database (Table 2). The percentage of pregnancies where the woman received only a single AED prescription during the entire 21-month time period was lowest in Denmark (17.4%) and highest in Tuscany (43.7%). Variations were observed in the time period when the woman was identified as receiving an AED prescription. In Denmark, Norway, Wales and the rest of the UK, approximately 75-79% of women identified as receiving an AED prescription received one during the 6 months before pregnancy, compared with 60-61% in Tuscany and the Netherlands (Table S2). Subsequently Tuscany and the Netherlands had a larger percentage of women who only received a prescription during the 6 months following the end of pregnancy. The percentage of women who received a prescription during pregnancy but not during the 6 months before pregnancy ranged from 8.4% in the UK to 15.1% in Tuscany.

---------- Insert Table 2 and Figure 1 here ---------

The percentage of AED exposed deliveries accounted for by the 5 most commonly prescribed AEDs, during each of the time periods, is shown in Figure 2. In the Danish and Norwegian databases, lamotrigine was clearly the drug of choice and the Danish database had the lowest levels of carbamazepine and valproate prescribing during pregnancy (Figure 2). In the UK databases lamotrigine was also the most frequently prescribed AED, followed more closely by carbamazepine and valproate. The trends observed in the Italian databases

differed from those observed in Northern Europe, with carbamazepine, valproate and phenobarbital being more popular. Differences were observed between the two Italian databases, with phenobarbital being the most popular during pregnancy in Tuscany whilst in Emilia Romagna it was carbamazepine. Carbamazepine was the most commonly prescribed AED in the Netherlands, although here the prescribing of lamotrigine did increase during early pregnancy. No clear trends were observed, in any database, in relation to choice of AED and maternal age.

---------- Insert Figure 2 here ----------

Of the newer AEDs, lamotrigine was the most commonly prescribed in all regions. Denmark was the only region where the percentage of oxcarbazepine exposures was higher than carbamazepine. In all regions, the use of topiramate, gabapentin and pregabalin declined during pregnancy whilst the use of lamotrigine and levetiracetam increased.
The majority of women were treated with AED monotherapy. In Wales, approximately 30% of AED users received prescriptions for two or more different AEDs during a 3-month time period whilst elsewhere it was between 10% and 20% (Figure S1). Prescribing of valproate during the first trimester in addition to another AED ranged from 2.0% (CI_{95}1.2-2.7%) of all AED exposed pregnancies in Denmark to 4.3% (CI_{95}2.8-5.9%) in Tuscany.

During the study period, a steady increase in the percentage of pregnancies where the woman received a prescription for lamotrigine during pregnancy was observed in Denmark, Tuscany and the Netherlands (Figure S2). In all regions, with the exception of Emilia Romagna, the proportion of AED exposed pregnancies receiving a prescription for valproate declined, whilst carbamazepine prescribing also declined in Denmark, Norway and Wales. During pregnancy, in Denmark and the UK a steady increase was observed in pregabalin and levetiracetam prescribing, whilst in Tuscany a decline in gabapentin and an increase in topiramate was observed. In the UK and Danish databases an increase in topiramate prescribing was observed between 2004 and 2007 followed by a decline from 2008.

Standard dose folic acid (≤0.5mg) was available over-the-counter in all regions, whereas high dose folic acid (>0.5mg) was only available on prescription. In Norway, the higher dose

prescribed was typically 1mg whilst elsewhere it was 5mg. No folic acid data were available for this study for Denmark. During the 3 months before pregnancy, the percentage of AED exposed pregnancies where the woman received a high dose folic acid prescription ranged from 1.0% (CI_{95}0.3-1.8%) in Emilia Romagna to 33.5% (CI_{95}28.7-38.4%) in Wales. During the first trimester these increased to 6.1% (CI_{95}4.1-8.2%) and 66.3% (CI_{95}61.2-71.4%) respectively (Figure 3a). In Tuscany, co-prescribing of folic acid was largely not until after the start of pregnancy and usually at the lower ≤0.5mg dose (Figure 3b). During the 3 months before pregnancy fewer than 50% of women received a prescription for folic acid of any dose.

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Discussion

Geographic variations were identified in the prevalence of AED prescribing and the AEDs most commonly prescribed before, during and after pregnancy. In all databases, prescribing declined during pregnancy. In Denmark, Norway and the UK, lamotrigine was clearly the AED of choice whilst in the Netherlands and Italian regions the older AEDs were more popular. Prescribing of folic acid during the 3 months before pregnancy was below 50% in all databases.

This study captured almost 11,000 deliveries, between 2004 and 2010, where the woman received an AED prescription during pregnancy or in the 6 months either side of pregnancy. Prescribing information was recorded independently of the women, removing recall bias; however no data were available on adherence and whether the woman actually took the medicine. In the UK databases, data were based on prescriptions issued in primary care whereas in other regions it was prescriptions dispensed by a pharmacist. Some women who are issued prescriptions may choose not to have them dispensed; this is less likely for AEDs prescribed for epilepsy, than for other indications, owing to the need to maintain good seizure control. None of the databases captured medicines given directly to the patient during a hospital stay. In Denmark, Norway and the Netherlands all other AED prescribing was captured. In the UK databases, prescriptions initiated by a specialist in a hospital

outpatient department and private prescriptions were rarely recorded; these numbers were likely to be small as most subsequent repeat prescribing will have been undertaken in primary care and private practice is limited. In Italy, only prescriptions reimbursed by the Italian healthcare system were captured, this excluded private prescriptions and the majority of prescriptions issued in secondary care, unless following the appointment the patient took the prescription to their GP and the GP prescribed it. In Emilia Romagna, prescriptions dispensed at a hospital pharmacy were also not captured during the study period; based on data from 2011, when this data started to be included in the database, the percentage of non-private prescriptions from a hospital pharmacy was approximately 30% of all AED prescriptions (A Puccini - personal correspondence). Increased availability of hospital dispensing data would allow maternal exposure to AEDs to be measured more accurately.

When exploring exposure patterns for women receiving prescriptions for more than one AED during a 3-month time period, this study did not differentiate between those who were taking them concomitantly and those switching between products. This study looked at the time period when a prescription was issued/dispensed, irrespective of duration. It is possible that some women will have received a prescription during one 3-month time period and continued taking it during the following period, even though they did not receive a further prescription, which may have resulted in some exposure status misclassification. For chronic conditions, such as epilepsy, this is likely to have had less of an impact than for episodic conditions. Bias may also have been introduced if the average prescription duration differed between regions, as this could have resulted in women in regions with a longer prescription duration (3 months or greater) contributing exposure information to fewer time periods than women in regions with a shorter prescription duration, even though they were continuously exposed.

For all deliveries, this study looked at prescribing during pregnancy as well as prescribing during the 6 months before and after pregnancy. In approximately 6.5% of pregnancies, part of the 6-month time period following a pregnancy overlapped to some extent with part of the 6-month time period before the start of a subsequent pregnancy or during part of the subsequent pregnancy itself. This will not have influenced the choice of prescribing during

the actual pregnancy itself but for a small number of pregnancies exposure during part of the 6-months following delivery may actually have been influenced by the fact that the mother had become pregnant. This study was not able to examine the clinical indication for prescribing as this was not fully available within the databases; this is a common limitation of electronic healthcare and claims databases. AEDs may be prescribed for several indications other than epilepsy, including psychiatric conditions where doses may be lower and polytherapy with other medicine classes is common. For AEDs prescribed to treat non-epilepsy indications it is possible that the choice of AED may have been selected for their relatively low potential for drug interactions rather than their pharmacodynamic profile. The regional variation observed in the time at which women received an AED prescription may suggest differences in the indication for prescribing, with those regions with a higher percentage of women receiving a prescription only during the 6 months after pregnancy, and not before or during pregnancy, indicating a greater level of prescribing for non-epilepsy indications. There is a need for more data sources that contain data on the indication for prescribing, especially for safety studies where there is the possibility of confounding by indication.

The popularity of the newer AEDs observed in Denmark was in line with another study, published by the European and International Registry of Antiepileptic drugs in Pregnancy (EURAP).[24] The use of lamotrigine in Norway was found to be higher in our study than the EURAP study, although this is likely due to the EURAP study covering an earlier time period (1999-2005). The lower use of the newer AEDs and higher use of phenobarbital in the Italian databases was in line with the EURAP study[24] and also with two Italian studies examining AED prescribing among the general population.[25-27] In our study population, we did not observe a similarly high prescribing rate of gabapentin in Italy,[25, 26] which is likely because this is most commonly prescribed for neuropathic pain in women older than childbearing age.[27] In Denmark, the higher use of oxcarbazepine is likely to reflect the fact that it became available in 1980,[28] whilst in other regions it was not until the 1990s. Our study had the strength of being population-based whilst pregnancy registry studies, such as those of EURAP,[24] reflect a sample of women who have self-enrolled or been enrolled by healthcare professionals. This selective enrolment has the potential to result in an over-representation of women taking newer AEDs or women with more severe medical conditions and may

mean their findings are not generalizable to all AED users. The AED utilisation figures for the UK databases during pregnancy were comparable to those of another study carried out in the UK using The Health Improvement Network database.[29] The prescribing of AEDs in all regions was lower than those reported in the United States, where a study evaluating administrative health plan data reported that for approximately 2% of deliveries between 2001 and 2007 the woman received at least one AED prescription during pregnancy or the 60 days before pregnancy.[30] In the US study, psychiatric conditions and pain disorders were reported to be more common indications for AED prescribing than epilepsy.[30]

The prescribing guidelines for all countries recommended that women taking AED therapy, who are considering becoming pregnant, aim for monotherapy treatment at the lowest effective dose.[10, 31-34] All guidelines acknowledged the increased risks of some major congenital anomalies and neurodevelopmental problems associated with valproate exposure during pregnancy[4, 35] and the increased risk of neural tube defects associated with carbamazepine.[3] It is therefore unclear what is continuing to drive the higher use of carbamazepine and valproate in Italy. The Italian guidelines were the only ones not to refer to an increased risk of congenital anomalies associated with phenobarbital. Two studies have shown phenobarbital to be one of the most commonly prescribed AEDs in Italy generally, at least until 2005.[25, 26] In Italy, due to the lack of conclusive evidence, until recently, of the teratogenicity of phenobarbital,[36] it was generally not withdrawn in women considering becoming pregnant. Italian neurologists would rather advise women to switch to phenobarbital from drugs known to be teratogenic (i.e. valproate) or those where little information was known, such as the newer AEDs (B Mostacci - personal correspondence). The findings of this study suggest that although the use of phenobarbital has declined over time, this practice may still be taking place. Although lamotrigine is demonstrating a better safety profile, in terms of tolerability and the risk of congenital anomalies in the offspring, the changes in endocrine and electrolyte balance and pharmacokinetics that occur in pregnancy can increase the risk of seizures[37, 38] and it is possible that these potential risks are perceived differently in different regions. Differences observed may also reflect differences in prescribing guidelines, the age of women when starting treatment, local custom and practice, costs of AEDs, timing of AED introduction to the market, drug promotion[24] and the type of prescriber.[39]

During the study period in Denmark, Italy and the UK, it was recommended that all women prescribed AEDs took high dose folic acid (4-5mg) before pregnancy, with continuation into the first trimester.[10, 31, 40] Folic acid supplementation was recommended at a standard 0.5mg dose in the Netherlands. In Norway, a minimum of 0.4mg was stated with a higher dose (4mg) recommended for women prescribed valproate or carbamazepine. Despite these recommendations, we found no evidence that co-prescribing of folic acid was usual practice during the pre-conception period. It is possible that some women may have purchased standard dose folic acid without a prescription which would not have been captured in the databases but this would not have given the recommended higher dose. Preconception care to review medication is increasingly being recommended and organised for women with epilepsy, while the situation regarding psychiatric care is less clear.

Conclusion

The regional differences in prescribing patterns identified suggest different use, knowledge or interpretation of the scientific evidence base, and are unlikely to reflect informed choice of women. The decline in AED prescribing during pregnancy and the low co-prescribing of folic acid suggest that many pregnancies were either unplanned or that full preconception care, including review of optimal AED medications for pregnancy, was not received by many women. Further research into the indications for which specific AEDs are prescribed during pregnancy is needed. This may help identify areas where more could be done to better inform clinicians and women of childbearing age taking AEDs of the need to plan their pregnancy and seek and receive complete preconception care.

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Table 1 Overview of databases contributing to the study

Country/Region	Netherlands	Denmark	Norway	Italy - Emilia Romagna	Italy - Tuscany	United Kingdom[1]	Wales
Involves database linkage	No	Yes	Yes	Yes	Yes	No	Yes[2]
Coverage	Regional	National	National	Regional	Regional	~8.5% sample of UK population	~40% sample of GP practices in Wales
Population base	500,000	~5,000,000	~4,800,000	4,200,000	3,700,000	~5,000,000[3]	2,000,000
Database for live & stillbirth pregnancy identification	IADB.nl database	Danish National Birth Registry	Medical Birth Registry of Norway	Certificate of Delivery Assistance (CeDAP)	Certificate of Delivery Assistance (CeDAP) Hospital Discharges Registry	Clinical Practice Research Datalink (CPRD)[4]	National Community Child Health Database (NCCHD)
Database for medicine use data	IADB.nl database	Danish Prescription Registry	Norwegian Precsription Database	Emilia-Romagna Prescription Database (ERPD)	Tuscany Prescription Database (TPD)	Clinical Practice Research Datalink	The General Practice (GP) Dataset
Source for medicine use data	Pharmacy dispensing	Pharmacy dispensing	Pharmacy dispensing	Pharmacy dispensing[5]	Pharmacy dispensing and Healthcare Facilities Dispensing[5]	GP practice prescribing	GP practice prescribing
Capture GP prescribing	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Capture hospital inpatient prescribing	No	No	No	No	No	Some	Some
Date of last menstrual period recorded	Estimated for all	Calculated from gestational age	Yes	Calculated from gestational age	Calculated from gestational age	Yes for 40% Estimated for 60%	Yes for 80% Estimated for 20%
Recommendations for folic acid use in women prescribed AEDs planning a pregnancy	Standard dose (0.5mg) before pregnancy and during first trimester.	High dose (5mg) before pregnancy and during first trimester	Standard dose (0.4mg) before pregnancy and during first trimester. High dose (1.0-4.0mg) for women prescribed valproic acid or carbamazepine.	High dose (4-5mg) before pregnancy and during first trimester	High dose (4-5mg) before pregnancy and during first trimester	High dose (5mg) before pregnancy and during first trimester	High dose (5mg) before pregnancy and during first trimester
Capture standard dose folic acid	No	No	Most	Some when prescribed	Some when prescribed	Some when prescribed	Some when prescribed
Capture high dose folic acid	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[1] Excluding practices in Wales to avoid duplication of pregnancies in the database contributing data for Wales
[2] Secure Anonymised Information Linkage (SAIL) databank
[3] The size of the population captured by the CPRD has grown steadily over time and was approximately 5.0 million in May 2012
[4] Previously the General Practice Research Database (GPRD)
[5] Only products reimbursed by the Italian National Health Service

Table 2 Prevalence of AED prescribing in women with a delivery between 2004 and 2010

Country/region	Number of eligible deliveries in entire cohort	Mean maternal age at pregnancy start for entire cohort		AED prescription during								
				the 6 months before pregnancy		any of the pregnancy trimesters		the 6 months following pregnancy		any of the time periods		
	N	Years	SD*	Per 10,000	(95% CI)	Per 10,000	(95% CI)	Per 10,000	(95% CI)	N	Per 10,000	(95% CI)
Denmark‡	324,134	30.0	[4.9]	54	(51 - 57)	46	(44 - 49)	46	(44 - 48)	2,207	68	(65 - 71)
Italy – Tuscany	157,916	31.8	[4.9]	77	(73 - 82)	56	(52 - 59)	65	(61- 69)	2,014	128	(122 - 133)
Italy – Emilia Romagna	149,485	32.2	[5.0]	62	(58 - 66)	44	(41 - 48)	48	(44 - 51)	1,357	91	(86 - 96)
Norway≠	330,758	29.7	[5.1]	64	(61 - 67)	49	(47 - 52)	50	(47 - 52)	2,815	85	(82 - 88)
The Netherlands	14,725	29.4	[4.8]	56	(44 - 68)	43	(33 - 54)	51	(39 - 62)	119	81	(66 - 95)
United Kingdom*	207,570	30.1	[6.0]	68	(64 - 71)	58	(55 - 62)	66	(62 - 69)	1,874	90	(86 - 94)
Wales	64,125	27.6	[6.1]	66	(60 - 73)	60	(54 - 66)	64	(58 - 71)	572	89	(82 - 96)
Total across countries	**1,248,713**			**64**	**(62 - 65)**	**51**	**(49 - 52)**	**54**	**(52 - 55)**	**10,958**	**88**	**(86 - 89)**

† Standard deviation

‡ 1 January 2004 – 31 December 2009

≠ 1 July 2004 – 31 December 2010

* Excluding Wales to avoid duplication of pregnancies in the Welsh SAIL databank

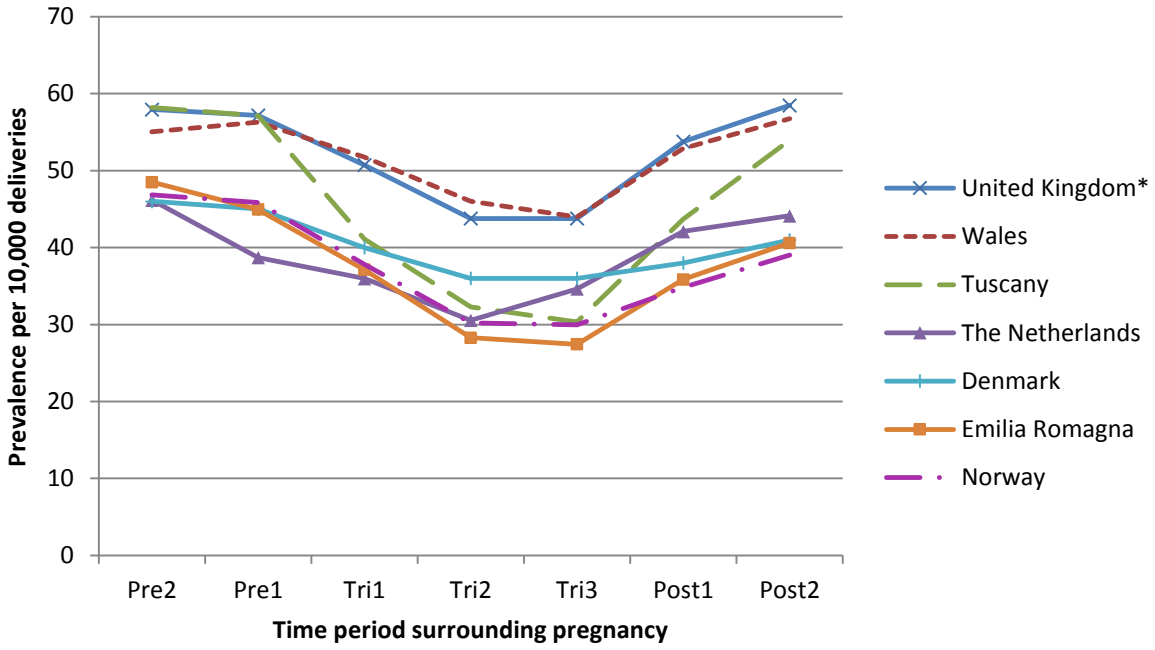
Figure titles

Figure 1 Prevalence of AED prescribing, per 10,000 deliveries, between 2004 and 2010

Figure 2 Percentage of all AED exposed deliveries prescribed the 5 most commonly prescribed AEDs in each region between 2004 and 2010

Figure 3 Percentage of AED exposed deliveries where the women was co-prescribed folic acid during the time period of interest

Figure 1



* excluding Wales

Figure 2

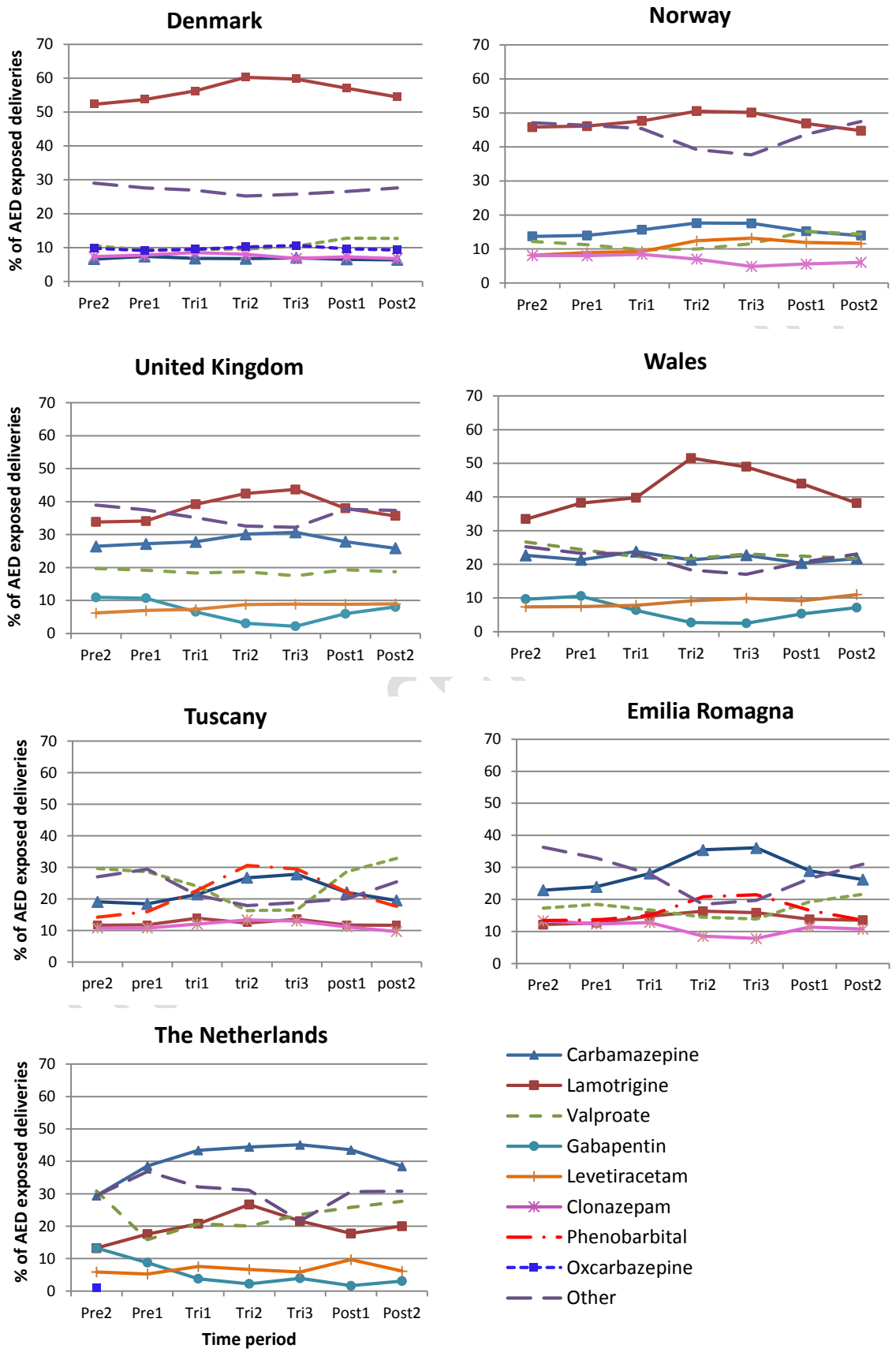
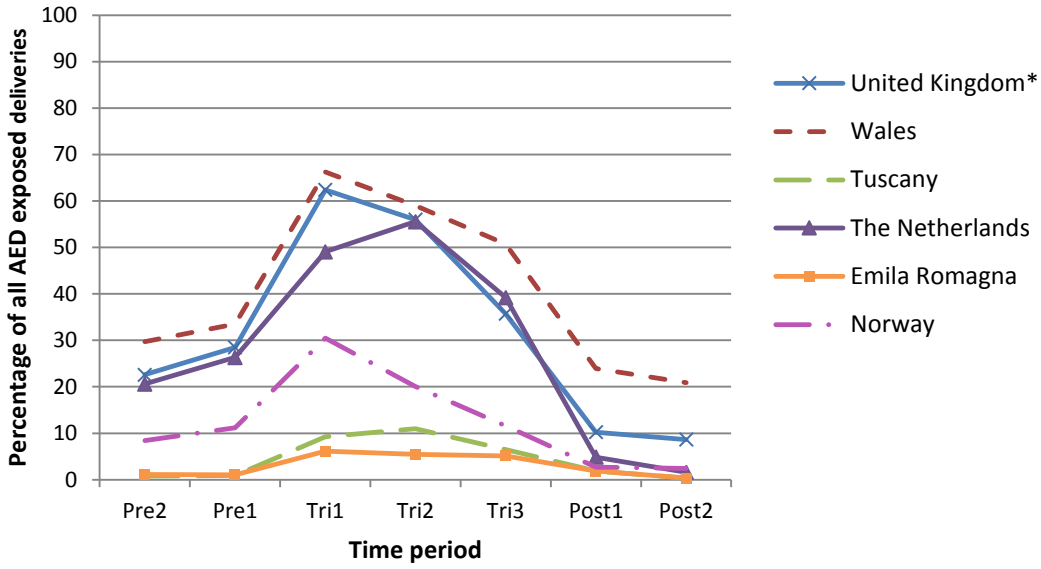

Denmark
Norway
United Kingdom
Wales
Tuscany
Emilia Romagna
The Netherlands
% of AED exposed deliveries
0
10
20
30
40
50
60
70
Pre2
Pre1
Tri1
Tri2
Tri3
Post1
Post2
pre2
pre1
tri1
tri2
tri3
post1
post2
Time period
Carbamazepine
Lamotrigine
Valproate
Gabapentin
Levetiracetam
Clonazepam
Phenobarbital
Oxcarbazepine
Other

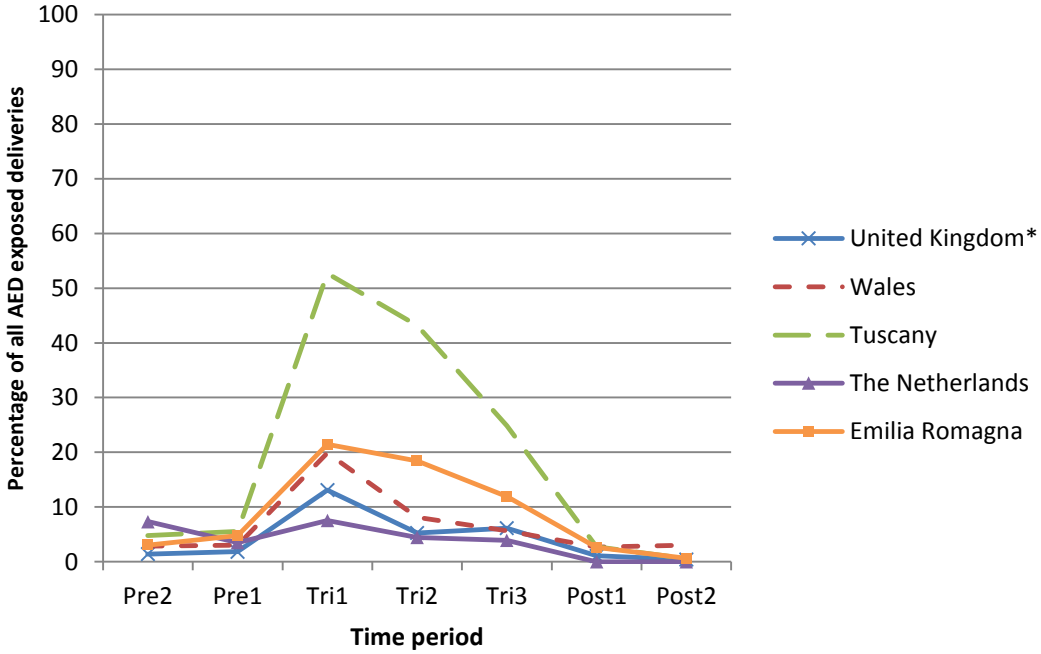
Figure 3

a) high dose folic acid (>0.5mg†)



* excluding Wales. † In Norway this was almost entirely for 1mg whilst in other countries it was largely 5mg

b) standard dose folic acid (≤0.5mg)



* excluding Wales

Standard dose folic acid purchased over-the-counter without a prescription was not captured in any region, however, prescriptions issued for standard dose folic acid were captured in all regions apart from Norway. No folic acid data were available for this study from Denmark.

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Figures for online only

Figure S1 Percentage of AED exposed pregnancies where the woman was prescribed an AED as monotherapy

Figure S2 Changes in AED prescribing during pregnancy between 2004 and 2009 for the 6 most commonly prescribed AEDs in 2009

Table for online only

Table S1 Availability of AEDs during the study period in each region

Table S2 Percentage of pregnancies where the woman received her first AED prescription during each of the time periods of interest

Figure S1

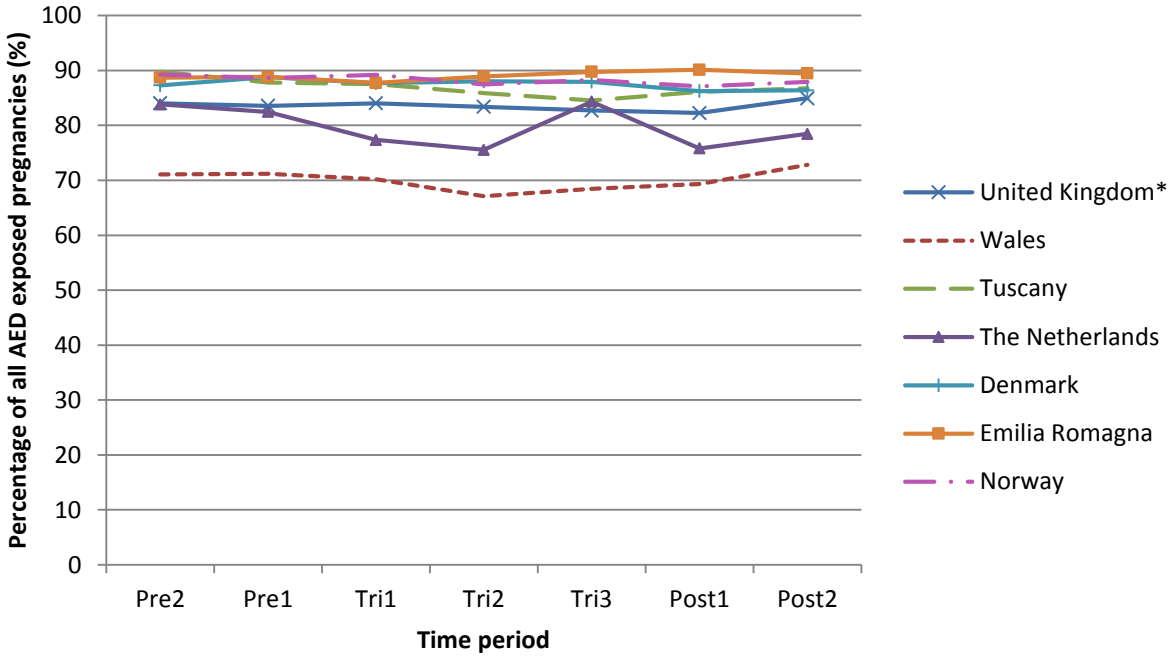

Figure S2

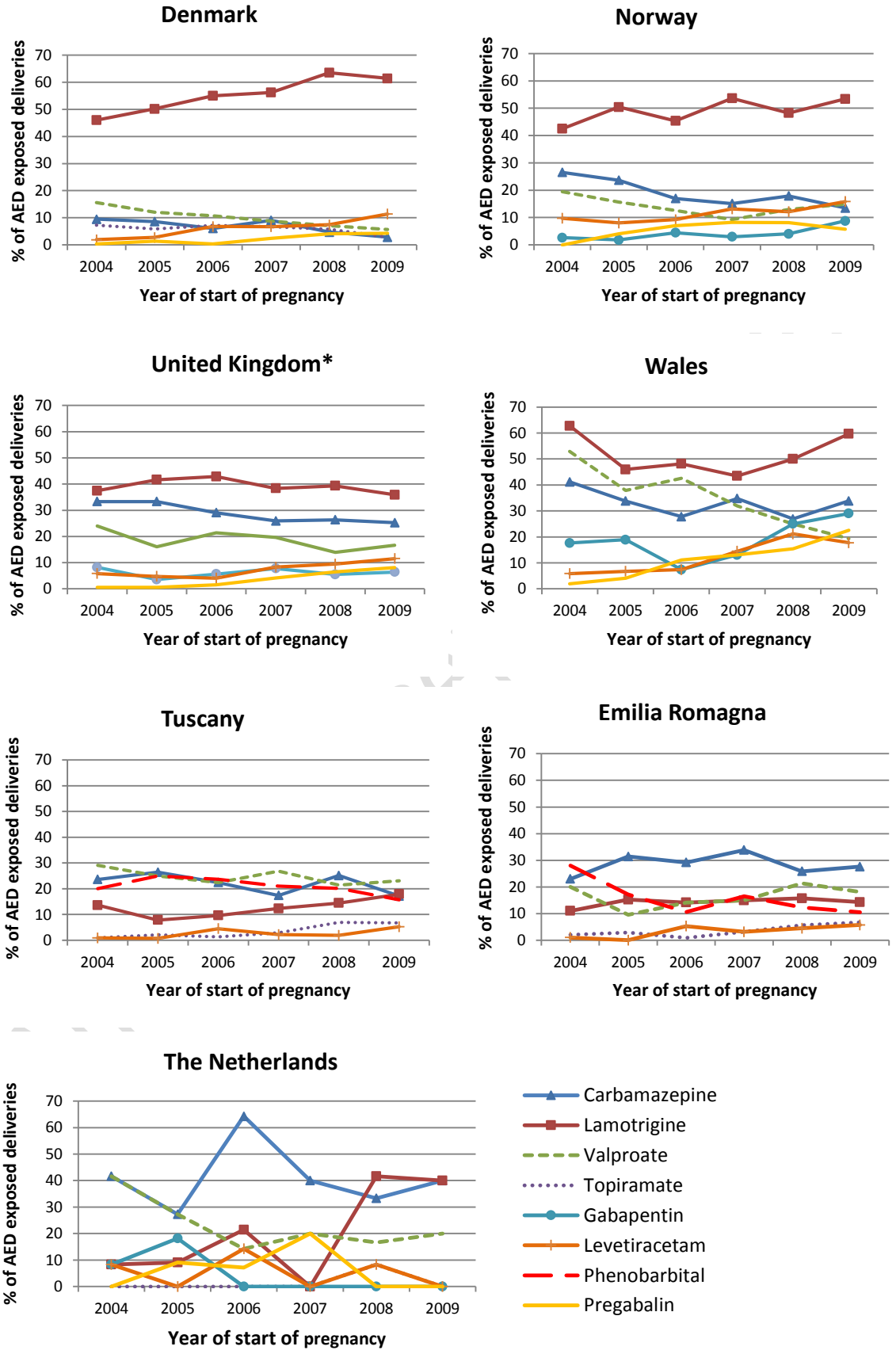
Denmark
Norway
United Kingdom*
Wales
Tuscany
Emilia Romagna
The Netherlands
% of AED exposed deliveries
Year of start of pregnancy
0
10
20
30
40
50
60
70
2004
2005
2006
2007
2008
2009
Carbamazepine
Lamotrigine
Valproate
Topiramate
Gabapentin
Levetiracetam
Phenobarbital
Pregabalin

Table S1 Availability of AEDs during the study period in each region

		Available during the study period						
ATC code	**Name**	**Denmark**	**Emilia Romagna**	**Norway**	**The Netherlands**	**Tuscany**	**United Kingdom**	**Wales**
N03AA01	Methylphenobarbital	N	N	N	N	N	N	N
N03AA02	Phenobarbital	Y	Y	Y	Y	Y	Y	Y
N03AA03	Primidone	Y	Y	Y[6]	Y	Y[7]	Y	Y
N03AA04	Barbexaclone	N	Y	N	N	Y	N	N
N03AA30	Metharbital	Y	N	N	N	N	N	N
N03AB01	Ethotoin	N	N	N	Y	N	N	N
N03AB02	Phenytoin	Y	Y	Y	Y	Y	Y	Y
N03AB03	Amino (diphenylhydantoin) valeric acid	N	N	N	N	N	N	N
N03AB04	Mephenytoin	N	N	N	N	N	N	N
N03AB05	Fosphenytoin	Y	Y[8]	N	N	N	Y	Y
N03AB52	Phenytoin combinations	N	N	N	N	Y	N	N
N03AB54	Mephenytoin combinations	N	N	N	N	N	N	N
N03AC01	Paramethadione	N	N	N	N	N	N	N
N03AC02	Trimethadione	N	N	N	N	N	N	N
N03AC03	Ethadione	N	N	N	N	N	N	N
N03AD01	Ethosuximide	Y	Y	N	Y	Y	Y	Y
N03AD02	Phensuximide	N	N	N	N	N	N	N
N03AD03	Mesuximide	N	N	N	N	N	N	N
N03AD51	Ethosuximide combinations	N	N	N	N	N	N	N
N03AF01	Carbamazepine	Y	Y	Y	Y	Y	Y	Y
N03AF02	Oxcarbazepine	Y	Y	Y	Y	Y	Y	Y
N03AF03	Rufinamide	Y	Y[9]	N	Y[v]	Y[10]	Y[v]	Y[v]
N03AF04	Eslicarbazepine	Y	N	Y*[11]	Y[vii]	N	Y[12]	Y[vii]
N03AG01	Valproic acid	Y	Y	Y	Y	Y	Y	Y
N03AG02	Valpromide	N	Y	N	N	Y	N	N
N03AG03	Aminobutyric acid	N	Y	N	N	Y	N	N
N03AG04	Vigabatrin	Y	Y	Y	Y	Y	Y	Y
N03AG05	Progabide	N	N	N	N	N	N	N
N03AG06	Tiagabine	N	Y	N	N	Y	Y	Y
N03AX03	Sultiame	N	N	N	N	N	N	N

[6] 2004-2007
[7] From 2005
[8] Hospital only
[9] From 2008
[10] From 2007
[11] From 2010
[12] From 2009

N03AX07	Phenacemide	N	N	N	N	N	N	N
N03AX09	Lamotrigine	Y	Y	Y	Y	Y	Y	Y
N03AX10	Felbamate	N	N	Y[13]	Y[ix]	Y	Y*[14]	Y[ix]
N03AX11	Topiramate	Y	Y	Y	Y	Y	Y	Y
N03AX12	Gabapentin	Y	Y	Y	Y	Y	Y	Y
N03AX13	Pheneturide	N	N	N	N	N	N	N
N03AX14	Levetiracetam	Y	Y	Y	Y	Y	Y	Y
N03AX15	Zonisamide	Y[15]	Y	Y	Y	Y[x]	Y	Y
N03AX16	Pregabalin	Y	Y	Y	Y	Y	Y	Y
N03AX17	Stiripentol	Y[16]	Y*[17]	N	Y	N	N	N
N03AX18	Lacosamide	Y[18]	Y	N	Y	Y[xiii]	Y	Y
N03AX19	Carisbamate	N	N	N	N	N	N	N
N03AX21	Retigabine	N	N	N	Y	N	N	N
N03AX30	Beclamide	N	N	N	N	N	N	N
N05BA01	Diazepam – rectal and parenteral only	N	Y	Y	Y	Y	Y	Y
N05BA06	Lorazepam - injection only	N	Y[19]	N	Y	Y	Y	Y
N05BA09	Clobazam	Y	Y	Y	Y	Y	Y	Y
N05CD08	Midazolam – buccal and nasal only	N	Y	Y[20]	N	N	Y	Y
N03AE01	Clonazepam	Y	Y	Y	Y	Y	Y	Y
N05CC05	Paraldehyde - rectum only	N	N	N	N	N	Y	Y

[13] From 2005
[14] From 2009
[15] From 2005
[16] From 2007
[17] From 2009, hospital prescribing only
[18] From 2008
[19] Hospital prescribing only
[20] From 2006-2007

Table S2

Country/region	First AED prescription during 6 months pre-preg		During preg		6 months post preg		Total AED
	N	%	N	%	N	%	
Denmark	1750	79.3	203	9.2	254	11.5	2,207
Italy – Tuscany	1220	60.6	304	15.1	490	24.3	2,014
Italy – Emilia Romagna	933	68.8	182	13.4	242	17.8	1,357
Norway[≠]	2124	75.5	312	11.1	379	13.5	2,815
The Netherlands	73	61.3	12	10.1	34	28.6	119
United Kingdom	1409	75.2	157	8.4	308	16.4	1,874
Wales	426	74.5	59	10.3	87	15.2	572